Sotos syndrome

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MJAFI 2011;67:288–290

INTRODUCTION

Sotos syndrome (also known as cerebral gigantism) is a rare genetic disorder characterised by excessive physical growth during the first 2–3 years of life. The disorder may be accompanied by mild mental retardation, hypotonia, speech impairment and delayed motor-cognitive-social development.¹ Children with Sotos syndrome are large at birth and all anthropometric parameters, including head circumference, are increased. Clumsiness, an awkward gait, and unusual aggressiveness or irritability may occur. Although most cases of Sotos syndrome occur sporadically, familial cases (autosomal dominant inheritance) have also been reported.

CASE REPORT

Case 1

A three-year-eight-month old girl was seen in the OPD, with history of excessive growth and an attack of generalised seizure (suggestive of febrile seizure). She was born at term, out of first-degree consanguineous marriage to a 25-year-old primigravida mother, by normal vaginal delivery. She weighed 3600 g at birth and had a head circumference of 38.5 cm (>2 SD). During the neonatal period, she had feeding difficulties, and was given top-feeds with spoon. She also had increased neonatal jaundice, which was managed with phototherapy. Review of old records of anthropometry revealed a rapid increase in weight and head circumference. Her father was 28 years of age and had an average built. Two of her cousins also had accelerated growth compared to their peers. All the milestones of the child were significantly delayed. Denver development screening test revealed a DQ of 78 (language more affected than motor). On physical examination, her weight was 25 Kg, height of 123 cm (US/LS: 1.24), head circumference was 55 cm (all were >3 standard deviation above mean for age), arm span was 128 cm and BMI of 16.7. She had prominent forehead, large ears (7 cm

long and 4.5 cm wide; Normal length: 5.5–6.5 cm and width: 3–4.5 cm), acral enlargement (hand and feet length of 12 and 15 cm, respectively) and sexual maturity rating (SMR) of 1 (Figure 1). There were no cranial nerve palsies. Muscle tone and deep tendon reflexes were normal. There was no macroglossia or organomegaly. Other systemic examination was unremarkable.

Complete blood counts, serum electrolytes, BUN, creatinine, fasting blood sugar, liver enzymes and thyroid profile were normal. Oral glucose tolerance test (OGTT) for growth hormone (GH) is shown in Table 1 which indicated suppression of GH (normal response) and normal glucose.

Hand radiograph indicated advanced bone age of 7 years 10 months, with seven carpal bones. Orthopaedics association in form of scoliosis, hip dislocation and genu vara/valga was excluded clinically. EEG, USG KUB, echocardiography and CT scan brain was normal.

Figure 1 (A, B) Case 1 with characteristic features of Sotos syndrome.

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Received: 21.01.2009; Accepted: 08.04.2011

doi: 10.1016/S0377-1237(11)60067-1

Table 1 OGTT – GH response.

Time (min)	BS (mg/dL)	GH (ng/mL)
0	69	0.33
30	53	0.51
60	85	0.32
90	65	0.84
120	89	0.59

BS: blood sugar; GH: growth hormone.

Case 2

A 6-year-5-month boy was seen in OPD, with typical phenotypic features of Sotos syndrome which included accelerated growth; with height (130 cm) (US:LS -0.85), head circumference (55.5 cm), weight (30.5 Kg) >3 SD above the mean and BMI of 18. He was the only child in the family, born out of non-consanguineous marriage. Birth and perinatal details were not available. He had coarse facial features, prominent forehead, macrocephaly, large ears (7 cm long and 4.8 cm wide) and hypertelorism (intercanthal distance of 34 mm; normal: 29.19 ± 3.36 mm) (Figure 2). There was no macroglossia or visceromegaly, and testes were normal. There was delay in expressive language and motor development, with IQ/DQ of 90. Bone age was advanced (of eight years). Routine biochemical parameters and thyroid assay was normal.

Both cases are being monitored regularly for speech, learning disability and other behavioural disorders. Echocardiography and renal ultrasound was done to rule out associated complications. Stimulation and physical therapy has been started for both cases, and speech therapy for the second case.

DISCUSSION

The patients we describe are typical cases of Sotos syndrome. Sotos syndrome is characterised by a distinctive facial appearance (prominent forehead, coarse facial features, macrocephaly and large ears), learning disability and overgrowth (height and weight 3 SD above the mean) resulting in tall stature, which is evident from birth. Sotos syndrome was first described in 1964 by Juan Sotos and the major diagnostic criteria of a distinctive facial appearance, childhood overgrowth and learning disability were established in 1994 by Cole and Sotos.^{1,2} NSD1 (nuclear receptor of SET domain containing protein) abnormalities, such as truncating mutations, missense mutations in functional domains, partial gene deletions and 5q35 microdeletions encompassing NSD1, are identifiable in the majority (>90%) of Sotos syndrome cases.^{3,4} The phenotype is largely independent of the underlying NSD1 defect, although cases with 5q35 microdeletions tend to have more severe learning disability and less pronounced overgrowth.^{5,6}

Sotos syndrome is reported to occur in 1 in 10,000 to 14,000 newborns. The “strict criteria” proposed for a diagnosis of Sotos

Figure 2 (A, B) Case 2 with prominent facial features of Sotos syndrome.

syndrome requires that the individual have at least three of the following⁶:

1. Facial appearance: large head, tall narrow skull, wide set down-slanting eyes, flat-bridged nose, high arched palate, early eruption of teeth (often by three months of age), thin hair, pointed chin, prominent forehead, and the appearance of a receding hairline.
2. Birth length above the 90th percentile.
3. Bone age above the 90th percentile.
4. Early verbal and motor delays.

The facial appearance is most distinctive between one and six years of age and consists of a high, broad forehead (the head is said to resemble an inverted pear), fronto-temporal hair sparsity, malar flushing, down-slanting palpebral fissures and a pointed chin (seen in our cases). In some children, there may be atypical features such as up-slanting palpebral fissures or a normal hairline. In adulthood, the appearance remains distinctive but the face is often longer and the chin more prominent.

The majority of individuals with Sotos syndrome have some degree of learning disability. Most individuals have mild-moderate intellectual impairment but the degree of impairment is extremely broad, ranging from occasional individuals with normal development to children with profound learning difficulties requiring life-long care.⁷ Poor coordination and occasional aggressiveness lead to problems of social adjustment. Frequent

behavioural issues include attention deficit hyperactivity disorder (ADHD), phobias, obsessions and compulsions, tantrums, and impulsive behaviours. Problems with speech and language are also common. Affected individuals often have problems with sound production, stuttering, and a monotone voice.

Many babies with Sotos syndrome have a birth length >2SD above the mean. The birth weight is often not proportionately increased and so babies with Sotos syndrome are usually long and thin. Before puberty the majority of children with Sotos syndrome have height and head circumference >2SD above the mean. There is often some 'normalisation' of height post-puberty so that the height of adults with Sotos syndrome may not be significantly above the norm. By contrast significant macrocephaly is typical in both children and adults with Sotos syndrome.

In the neonatal period, approximately 70% of babies with Sotos syndrome develop jaundice and/or have difficulty in feeding (due to neonatal hypotonia, which is very common as seen in Case 1). Cardiac and renal anomalies, seizures and scoliosis occur in 15–30% of cases and are very variable in type and severity.⁷ The cardiac anomalies range from single, self-limiting anomalies such as atrial septal defect to complex anomalies requiring interventional surgery. The most common renal abnormality is vesico-ureteric reflux, but anatomical abnormalities such as duplex kidney, absent kidney, urethral stenosis and pelvi-ureteric junction obstruction are also recognised. Infantile spasms, absence, tonic/clonic and myoclonic seizures are all described in Sotos syndrome.⁷

Advanced bone age occurs in approximately 75% of affected children. Many individuals with Sotos syndrome have abnormalities on cranial imaging. These are largely nonspecific.⁸ Ventricular dilatation is the most commonly reported feature.⁶ Children with Sotos syndrome do not have severe brain malformations. However, they usually have extra fluid on the surface of the brain, enlarged ventricles and absence or reduced size of the corpus callosum. The brain itself is normal size. The extra fluid, which fills up the space inside the skull, is not hydrocephalus.

Four conditions most commonly confused with Sotos syndrome are Weaver syndrome, Bannayan–Riley–Ruvalcaba syndrome, Beckwith–Wiedemann syndrome and benign familial macrocephaly.^{9,10} Other possibilities that can resemble this entity are Perlman syndrome, Simpson–Golabi–Behmel syndrome, Fragile X syndrome, PTEN mutations, Nevo syndrome, neurofibromatosis I, Marshall syndrome, Marfan syndrome, homocystinuria, and acromegaly.

Affected individuals should be counselled with an offspring risk of 50% as for other autosomal dominant conditions. The observed vertical transmission rate in Sotos syndrome is clearly lower than this as familial Sotos syndrome is rare, with less than 10% of cases having an affected relative.

There is no standard course of treatment for Sotos syndrome. Treatment is symptomatic. Programmes such as infant

stimulation, occupational therapy, physical therapy, speech therapy, and adaptive physical education play a significant role in the nurturing of a child with Sotos syndrome. In a structured environment, the child is able to practice necessary skills without excessive distractions. As with any child, self-esteem in a child with Sotos syndrome is bolstered by successful completion of tasks and mastery of developmental skills.

Sotos syndrome is not a life-threatening disorder and patients may have a normal life expectancy. The initial abnormalities of Sotos syndrome usually resolve as the growth rate becomes normal after the first few years of life. Developmental delays may improve in the school-age years, however, coordination problems may persist into adulthood.

This report highlights the importance of considering this diagnosis in children presenting with psychomotor delay, large stature and seizures. Though, Sotos syndrome is not a very rare entity; however, not many cases have been reported from India. Also, this diagnosis is commonly missed by medical practitioners.

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